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DOCKET NO.: PHOE-0060 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Mike A. Clark, Charles Mark Ensor,
Frederick Wayne Holtzberg

Confirmation No.: 9010

Application No.: 09/775,693

Group Art Unit: 1642

Filing Date: February 2, 2001

Examiner: Minh Tam B. Davis

For: Methods For Predicting Sensitivity Of Tumors To Arginine Deprivation

EXPRESS MAIL LABEL NO: EV 764535930 US
DATE OF DEPOSIT: March 15, 2006

EV764535930US

MS Appeal Brief - Patent
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF TRANSMITTAL PURSUANT TO 37 CFR § 1.192

Transmitted herewith in triplicate is the APPEAL BRIEF in this application with respect to the Notice of Appeal received by The United States Patent and Trademark Office on **December 15, 2005**.

☒ Applicant(s) has previously claimed small entity status under 37 CFR § 1.27 .

☐ Applicant(s) by its/their undersigned attorney, claims small entity status under 37 CFR § 1.27 as:

- ☐ an Independent Inventor
- ☐ a Small Business Concern
- ☐ a Nonprofit Organization.

☐ Petition is hereby made under 37 CFR § 1.136(a) (fees: 37 CFR § 1.17(a)(1)-(4) to extend the time for response to the Office Action of to and through comprising an extension of the shortened statutory period of month(s).

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	SMALL ENTITY		NOT SMALL ENTITY	
	RATE	FEE	RATE	FEE
☒ APPEAL BRIEF FEE	$250	$250.00	$500	$
☒ ONE MONTH EXTENSION OF TIME	$60	$60.00	$120	$
☐ TWO MONTH EXTENSION OF TIME	$225	$0.00	$450	$
☐ THREE MONTH EXTENSION OF TIME	$510	$0.00	$1020	$
☐ FOUR MONTH EXTENSION OF TIME	$795	$0.00	$1590	$
☐ FIVE MONTH EXTENSION OF TIME	$1080	$0.00	$2160	$
☐ LESS ANY EXTENSION FEE ALREADY PAID	minus	($0.00)	minus	($)
TOTAL FEE DUE		$310.00		$0

☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to Deposit Account 23-3050. This sheet is provided in duplicate.

☒ A check in the amount of **$310.00** is attached. Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

☐ Please charge Deposit Account No. 23-3050 in the amount of **$ .00**. This sheet is attached in duplicate.

☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

Date: March 15, 2006

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Mike A. Clark, Charles Mark Ensor, and Frederick Wayne Holtsberg**

Confirmation No.: **9010**

Serial No.: **09/775,693**

Group Art Unit: **1642**

Filing Date: **February 2, 2001**

Examiner: **Minh Tam B. Davis**

For: **Methods For Predicting Sensitivity Of Tumors To Arginine Deprivation**

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Mail Stop Appeal-Brief Patents
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APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. § 41.37

This brief is being filed in support of Appellant's appeal from the final rejection of claims 1, 2, 6, 7, 27, and 31 to 36 dated June 15, 2005. A Notice of Appeal was filed on December 13, 2005 and was received by the Patent Office on December 15, 2005.

1. REAL PARTY IN INTEREST

Based on information supplied and to the best of the undersigned's knowledge, the real party in interest in the above-identified patent application is the assignee, Phoenix Pharmacologics, Inc., a corporation of Delaware.

2. RELATED APPEALS AND INTERFERENCES

The undersigned and the assignee know of no other appeals or interferences that will directly affect, be directly affected by, or have a bearing on, the Board's decision in the pending Appeal.

3. STATUS OF CLAIMS

Claims 1, 2, 6, 7, 27, and 31 to 36 are pending in the present application and stand rejected. Appellants appeal the rejection of claims 1, 2, 6, 7, 27, and 31 to 36, which are listed in Appendix A.

4. STATUS OF AMENDMENTS

The claims were last amended on May 2, 2003, and the amendments were entered.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The selective depletion of amino acids from the circulation by the administration of amino acid degrading enzymes has been explored as a potential cancer treatment for at least the last 40 years. L-asparaginase has been used to lower circulating levels of asparagine in the treatment of acute lymphoblastic leukemia, and arginine-degrading enzymes have been postulated to hold promise as means for controlling melanoma, hepatoma, and some sarcomas. Human melanoma and hepatoma cells have been reported to be killed *in vitro* by the elimination of arginine from the medium in which the cells are grown. Melanoma and hepatoma cells implanted into mice have been reported to be killed by the administration of arginine deiminanse, an arginine degrading enzyme, to the mice. In addition, a number of other tumor types have been reported to be killed by arginine deiminase.

It has been demonstrated, however, that arginine deficiency results in undesired side effects in certain patients. In addition, it has been shown that arginine deprivation therapy is

not effective against all cancerous tumor types. Methods for determining which cancer patients would or would not be susceptible to arginine deprivation therapy would enable those in the medical community to efficiently initiate the appropriate course of treatment for cancer patients, while avoiding inappropriate or ineffective treatments for certain patients.

Applicants have developed methods for identifying cancer patients that are susceptible to arginine deprivation therapy that comprise obtaining a cancerous tumor sample from a cancer patient and detecting the presence or absence of argininosuccinate synthetase protein in the sample. The absence of argininosuccinate synthetase protein in the cancerous tumor sample is indicative of a cancer patient who is a candidate for arginine deprivation therapy, while the presence of argininosuccinate synthetase protein in the cancerous tumor sample is indicative of a cancer patient who is not a candidate for arginine deprivation therapy.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

One issue remains for resolution in this appeal:

Whether the Examiner has demonstrated that the subject matter of claims 1, 2, 6, 7, 27, and 31 to 36 would have been obvious to those of ordinary skill in the art in view of the combined teaching of U.S. Patent No. 5,804,183 ("the Filpula patent"), Takaku *et al., Jpn. J. Cancer Res.*, 1995, 86, 840-846 ("the Takaku reference"), Sugimura *et al. Melanoma Res.*, 1992, 2, 191-196 ("the Sugimura reference") and Oyanagi *et al., Tohoku J. Exp. Med.* (Japan), 1986, 148(4), 385-391 ("the Oyanagi reference").

7. ARGUMENT

The Examiner has not established that the subject matter of claims 1, 2, 6, 7, 27, and 31 to 36 would have been obvious to persons of ordinary skill in the art in view of the

combined teaching of the Filpula patent, the Takaku reference, the Sugimura reference, and the Oyanagi reference. To establish *prima facie* obviousness, the Patent Office must demonstrate that the cited prior art reference or combination of references teaches or suggests all the limitations of the claims,[1] which the Examiner has failed to do in the present case.

Applicants' claims recite methods for identifying cancer patients that are susceptible to arginine deprivation therapy that comprise obtaining a cancerous tumor sample from the patients and detecting the presence or absence of argininosuccinate synthetase protein in the tumor sample. The absence of argininosuccinate synthetase protein in the tumor sample is indicative of a cancer patient who is a candidate for arginine deprivation therapy, while the presence of argininosuccinate synthetase protein in the tumor sample is indicative of a cancer patient who is not a candidate for arginine deprivation therapy.

Such methods would not have been obvious to those of ordinary skill in the art at the time of the invention because, prior to Applicants' efforts, it had not been recognized or appreciated in the art that the level of argininosuccinate synthetase protein expressed in tumor cells could be used to predict whether particular tumors would be sensitive to arginine deprivation therapy. The art did not teach or suggest that the level of argininosuccinate synthetase protein in a cancerous tumor sample could be used to determine whether the patient from which the sample was obtained was a candidate for arginine deprivation therapy.

The Sugimura reference describes experiments in which the sensitivity of five human melanoma cell lines and one human carcinoma cell line to *Mycoplasma arginini* arginine deiminase was determined. The reported results indicate that the growth of cells of each of the melanoma cell lines was inhibited by arginine deiminase, although to varying degrees, but the growth of the carcinoma cells was not affected. Proliferation of the C32TG, Mewo, and

[1] *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

VMRG-MELG melanoma cells was inhibited by 16 ng/ml of arginine deiminase, and proliferation of the A375 melanoma cells was almost completely inhibited by 32 ng/ml of arginine deiminase.[2] The melanoma cell line G361 "also exhibited high sensitivity to AD, showing a marginal response (23% of control cell proliferation) at 130 ng/ml of AD."[3] In contrast, "[t]he growth of HeLa [carconima] cells was hardly affected by AD."[4] Further experiments were conducted to determine the level of argininosuccinate synthetase mRNA present in cells of each cell line, with the cell line TL-Mor serving as a positive control. Argininosuccinate synthetase transcripts were not detected in the C32TG, Mewo, and VMRC-MELG cells.[5] The level of argininosuccinate synthetase transcripts detected in A375 cells and G361 cells was 1/34 and 1/5, respectively, of that found in TL-Mor,[6] while the level of argininosuccinate synthetase transcripts in HeLa cells was 1/3 of that of TL-Mor.[7]

The level of argininosuccinate synthetase mRNA in the G361 melanoma cells was 20 % of that of the control cell line, but the G361 melanoma cells still exhibited "high sensitivity to AD."[8] In contrast, the level of argininosuccinate synthetase mRNA in the carcinoma cells was 33 % of that of the control cells, but the carcinoma cells were ***not*** sensitive to arginine deiminase. Those skilled in the art would have expected the carcinoma cells to exhibit sensitivity to arginine deiminase, in light of the fact that the G361 cells exhibited sensitivity, but had only slightly less argininosuccinate synthetase mRNA than the carcinoma cells. Based upon these results, at the time of the invention, those skilled in the art would not have concluded that the level of argininosuccinate synthetase expression in cells of different tumor

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[2] Page 193, first column, first full paragraph.
[3] *Id.*
[4] *Id.*
[5] Page 194, paragraph bridging columns 1 and 2.
[6] *Id.*
[7] *Id.*
[8] Page 193, first column, first full paragraph.

types could have been used to successfully predict whether particular tumors would be sensitive to arginine deiminase. The Sugimura reference, accordingly, does not suggest that argininosuccinate synthetase protein levels in a tumor sample derived from a cancer patient could be used to determine whether the patient would be a candidate for arginine deprivation therapy.

The remaining references do not compensate for the deficiencies of the Sugimura reference. The Takaku reference describes experiments demonstrating that *Mycoplasma arginini* arginine deiminase inhibited the growth of mouse hepatoma cells (MH143) and mouse fibrosarcoma cells (Meth A) by depleting arginine present in the medium in which the cells were grown.[9] The reference does not report the level of argininosuccinate synthetase expression in the hepatoma and fibrosarcoma cells, however. Nor does the reference teach or suggest that the level of argininosuccinate synthetase protein in cells of different tumor types could be assessed to determine which tumor types would be sensitive to the growth inhibitory activity of arginine deiminase.

The Filpula patent describes conjugation of *Mycoplasma arthritidis* arginine deiminase to polymers and teaches that the conjugates can be used to treat a variety of conditions that are known to respond to arginine deiminase deprivation therapy.[10] The patent states that such conditions include carcinomas that are deficient in argininosuccinate synthetase, such as the melanomas described by the Sugimura reference.[11] The Filpula patent thus teaches that *Mycoplasma arthritidis* arginine deiminase can be used to treat conditions that are known to respond to arginine deprivation, which include melanomas deficient in argininosuccinate synthetase. The patent does not independently report the level of argininosuccinate synthetase expression in carcinoma or melanoma cells, however, but cites

[9] Page 843, first and second columns and page 844, first column.
[10] Col. 13, lns. 6-15.
[11] Col. 13, lns. 15-19. Applicants note, however, that melanomas are not a type of carcinoma.

the Sugimura reference for the proposition that melanoma cells are deficient in argininosuccinate synthetase. Moreover, the patent does not teach or suggest that levels of argininosuccinate synthetase expression in different tumor types can be used to predict the sensitivity of particular tumors to arginine deiminase therapy. The patent, accordingly, does not teach or suggest that argininosuccinate synthetase protein levels in tumor cells from cancer patients should be determined in order to ascertain whether the patients would be sensitive to arginine deiminase treatment.

The Oyangi reference reports case studies of two patients suffering from citrullinemia, a metabolic disorder caused by argininosuccinate synthetase deficiency. One of the patients (case 2) was diagnosed with adult-type citrullinemia at age 27. Argininosuccinate synthetase activity in the liver tissues of the patient decreased to 20% of that of control liver tissues. The patient's liver progressively deteriorated, and the patient died of hepatoma at age 31. The reference does not teach or suggest that hepatomas are deficient in argininosuccinate synthetase, however, nor does it teach or suggest treating hepatoma with arginine deprivation therapy. The reference, accordingly, does not teach or suggest that levels of argininosuccinate synthetase expression in tumor cells can be used to predict the sensitivity of the cells to arginine deiminase therapy. The reference also does not teach or suggest that argininosuccinate synthetase protein levels in tumor cells of cancer patients should be measured to determine whether the patients are candidates for arginine deiminase therapy.

When the Sugimura reference, the Filpula patent, the Takaku reference, and the Oyanagi reference are combined, they fail to teach or suggest the claimed methods. The Sugimura reference teaches that the level of argininosuccinate synthetase mRNA present in cells of different cancer types does not correlate with the cells' sensitivity to arginine deiminase. The level of argininosuccinate synthetase mRNA in cells of the melanoma cell

line G361 was 20 % of that of cells of the control cell line, but the G361 cells still exhibited high sensitivity to arginine deiminase. In contrast, the level of argininosuccinate synthetase mRNA in cells of the carcinoma cell line HeLa was 33 % of that of cells of the control cell line, but the carcinoma cells were not sensitive to arginine deiminase. The Filpula patent teaches that polymer conjugates of arginine deiminase can be used to treat conditions known to respond to arginine deiminase therapy, such as melanoma as described in the Sugimura reference, but does not independently report the level of argininosuccinate synthetase expression in melanoma cells. The Takaku reference demonstrates that arginine deiminase inhibits the growth of mouse hepatoma and fibrosarcoma cells by depleting arginine, but does not report the level of argininosuccinate synthetase expression in the hepatoma and fibrosarcoma cells. The Oyangi reference describes a case study of adult citrullinemia and reports that the patient died of hepatoma after experiencing progressive liver deterioration, but does not report that hepatoma cells are deficient in argininosuccinate synthetase.

Accordingly, when the cited references are combined, they suggest that arginine deiminase may ***potentially*** be used to treat melanoma, hepatoma, or fibrosarcoma, due to the demonstration that such cells are sensitive to arginine deiminase. The references, however, ***do not*** teach or suggest that the level of argininosuccinate synthetase protein present in different types of tumor cells can be used to predict whether particular tumors will be sensitive to arginine deprivation therapy. Accordingly, the references fail to teach or suggest methods for identifying cancer patients susceptible to arginine deprivation therapy that involve determining the level of argininosuccinate synthetase protein present in tumor samples from the patients. The Examiner has, therefore, failed to establish that the claimed methods are *prima facie* obvious.

The Examiner incorrectly asserts that "high susceptibility to cell killing by AD therapy is correlated with low level of ASS, as taught by Sugimura et al."[12] As discussed above, the Sugimura references reports that the level of argininosuccinate synthetase mRNA in G361 melanoma cells was 20 % of that of the control cells, but the cells still exhibited high sensitivity to arginine deiminase, while the level of argininosuccinate synthetase mRNA in HeLa carcinoma cells was 33 % of that of the control cells, but the carcinoma cells were not sensitive to arginine deiminase. The Sugimura reference thus teaches that levels of argininosuccinate synthetase mRNA correlate with sensitivity to arginine deiminase in melanoma cells only, and reports that the correlation does not exist in carcinoma cells. Those skilled in the art would thus not have concluded, based upon the teachings of the Sugimura reference, that low levels of argininosuccinate synthetase are necessarily correlated with sensitivity to arginine deiminase in tumor types other than melanoma.

The Examiner further asserts that "AD therapy has been successfully used for treating carcinoma, or melanoma, all of which are deficient in ASS, as taught by Fipula et al." The Filpula patent states, however, that "arginine deiminase conjugates can be used to treat conditions, including, carcinomas deficient in the enzyme argininosuccinate synthetase, e.g., melanoma,"[13] citing the Sugimura reference. As discussed above, the Sugimura reference teaches that despite the fact that carcinoma cells exhibited reduced levels of argininosuccinate synthetase mRNA, the cells were not sensitive to arginine deiminase, unlike melanoma cells. Accordingly, the Sugimura reference does not teach or suggest that carcinoma cells deficient in argininosuccinate synthetase are sensitive to arginine deiminase, nor does the reference teach or suggest that carcinomas can be treated with arginine deiminase. The Filpula patent apparently incorrectly interpreted the teachings of the Sugimura reference.

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[12] Office Action dated June 15, 2005, page 3.
[13] *Id.*

Finally, the Examiner also incorrectly asserts that "the AD sensitivity of various tumor cells is attributed to the reduced level of argininosuccinate synthetase expression, as taught by Sugimura et al."[14] As discussed above, the Sugimura reference teaches only that melanoma cells that were deficient in argininosuccinate synthetase mRNA exhibited sensitivity to arginine deiminase. Carcinoma cells having reduced levels of argininosuccinate synthetase mRNA were not sensitive to argine deiminase. Sugimura thus does not teach that "various" tumor cells were sensitive to arginine deiminase. Nor would those skilled in the art have attributed arginine deiminase sensitivity to low levels of argininosuccinate synthetase expression, due to the fact that carcinoma cells exhibited low levels of argininosuccinate synthetase expression relative to control cells, but were not sensitive to arginine deiminase.

The Examiner has thus failed to demonstrate that the cited references teach or suggest all the limitations of the pending claims, and, therefore, has failed to establish *prima facie* obviousness.

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[14] *Id.*

8. CONCLUSION

For the foregoing reasons, Appellants request that the present patent application be remanded to the Examiner with an instruction to both withdraw the outstanding rejections, and to allow the appealed claims.

Respectfully submitted,

Date: March 15, 2006

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APPENDIX A

PENDING CLAIMS

1. A method for identifying a cancer patient susceptible to arginine deprivation therapy comprising the steps:

a) obtaining a cancerous tumor sample from the cancer patient; and

b) detecting the presence or absence of argininosuccinate synthetase protein in said cancerous tumor sample, wherein the absence of argininosuccinate synthetase protein in said cancerous tumor sample is indicative of a cancer patient who is a candidate for arginine deprivation therapy and the presence of argininosuccinate synthetase protein in said cancerous tumor sample is indicative of a cancer patient who is not a candidate for arginine deprivation therapy.

2. The method of claim 1 wherein prior to, simultaneous with, or after testing the cancerous tumor sample, the method further comprises the steps of:

c) obtaining a non-cancerous sample of the corresponding tissue from the cancer patient; and

d) detecting the presence or absence of argininosuccinate synthetase protein in said non-cancerous sample, wherein the absence of argininosuccinate synthetase protein in said non-cancerous sample and the absence of argininosuccinate synthetase protein in said cancerous tumor sample is indicative of a cancer patient who is not a good candidate for arginine deprivation therapy, wherein the presence of argininosuccinate synthetase protein in said non-cancerous sample and the absence of argininosuccinate synthetase protein in said cancerous tumor sample is indicative of a cancer patient who is a good candidate for arginine

deprivation therapy, and wherein the presence of argininosuccinate synthetase protein in said cancerous tumor sample is indicative of a cancer patient who is not a candidate for arginine deprivation therapy.

3-5. (canceled)

6. The method of claim 1 wherein the presence or absence of argininosuccinate synthetase protein is detected using a technique selected from the group consisting of Western blotting, ELISA, enzyme assays, slot blotting, electrophoresis, and immunohistochemistry.

7. The method of claim 1 wherein the presence or absence of argininosuccinate synthetase protein is detected using ELISA.

8-26. (canceled)

27. The method of claim 1 wherein argininosuccinate synthetase protein in said cancerous tumor sample is detected comprising the steps of:

a) contacting the cancerous tumor sample of the cancer patient with an antibody specific for an argininosuccinate synthetase protein, or portion thereof; and

b) detecting binding of the antibody to said argininosuccinate synthetase protein, or portion thereof, in said cancerous tumor sample wherein the absence of binding of the antibody to said argininosuccinate synthetase protein is indicative of a cancer patient who is a candidate for arginine deprivation therapy and the presence of binding of the antibody to said

argininosuccinate synthetase protein in said cancerous tumor sample is indicative of a cancer patient who is not a candidate for arginine deprivation therapy.

28-30. (canceled)

31. The method of claim 27 wherein said antibody has a detectable label.

32. The method of claim 31 wherein said detectable label is radioactive, fluorescent, or chromomorphic.

33. The method of claim 31 wherein said detectable label is ^{131}I, ^{125}I, ^{14}C, ^{35}S, ^{32}P, or ^{33}P.

34. The method of claim 31 wherein said detectable label is fluorescein, phycolipoprotein, or tetrarhodamine isothiocyanate.

35. The method of claim 31 wherein said detectable label is an enzyme.

36. The method of claim 31 wherein said detectable label has a visible color.